

Comparing the Efficacy of Methadone and Tincture of Opium in Controlling Agitation Caused by Withdrawal Syndrome in Opium-Addicted Patients in the Intensive Care Unit: A Randomized Trial Study

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Original Article

Abstract

Background: Few studies have been conducted regarding the comparison of the efficacy of methadone and tincture of opium (TOP) in controlling agitation induced by withdrawal syndrome. Therefore, the current randomized trial study is carried out with the aim to evaluate comparisons on the efficacy of methadone and TOP in controlling agitation caused by withdrawal syndrome in opium addicted patients in the intensive care units (ICUs).

Methods: This clinical trial study was conducted on 60 patients admitted to ICU of Shahid Bahonar Hospital, Kerman, Iran. After classification of the patients into two groups, the first and second groups consumed methadone syrup (5 mg/ml) and TOP (10 mg/ml), respectively. Agitation in these patients was assessed through the Richmond Agitation-Sedation Scale (RASS). Vital signs were also assessed. Paired sample t-test and independent t-test were used for data analysis.

Findings: In the current study, the administered dose of methadone and TOP was 36.17 ± 26.99 and 112.67 ± 102.74 mg, respectively ($P < 0.010$). Methadone administration led to a significant decrease of the patients' vital signs, including systolic blood pressure, heart rate, respiratory rate, and Glasgow Coma Scale (GCS) ($P < 0.05$). Though TOP administration decreased systolic blood pressure and GCS significantly ($P < 0.05$), it had no effect on patients' diastolic blood pressure, body temperature, heart rate, and respiratory rate ($P > 0.05$). In total, no significant difference was detected between two groups regarding vital signs ($P > 0.05$). However, a significant difference was seen between methadone and TOP groups in terms of RASS score ($P < 0.01$).

Conclusion: According to the results of the current study, lower dose of methadone, compared to TOP, could control agitation caused by opium withdrawal symptoms.

Keyword: Methadone; Opium dependence; Intensive care units

Citation: Sohrevardi SM, Pournamdari M, Salimi R, Sarrafzadeh F, Ahmadinejad M. **Comparing the Efficacy of Methadone and Tincture of Opium in Controlling Agitation Caused by Withdrawal Syndrome in Opium-Addicted Patients in the Intensive Care Unit: A Randomized Trial Study.** *Addict Health* 2020; 12(2): 69-76.

Received: 22.11.2019

Accepted: 18.01.2020

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Introduction

Opium is a substance extracted from opium poppy.¹⁻³ According to World Drug Report in 2015, approximately 16.5 million people use opiates, including opium and heroin.⁴ Consumption of opium is high in many south Asian countries, especially Afghanistan and Pakistan.¹ Opium is readily available in Iran due to long boundary between Afghanistan and Iran.^{5,6}

Bases on previous studies, there were more than one million opium addicts in Iran in 2003.⁷ Opium consumption in Iran is most prevalent in northern and southern cities.⁸ Opium intake is associated with injury, obesity, and poor quality of life (QOL).^{9,10} Moreover, opium consumption increases the risk of bladder, lung, laryngeal,⁷ and upper gastrointestinal cancers.⁸

Studies have shown that opium use cessation or reduction in the opium-dependent individuals leads to opium withdrawal syndrome.¹¹ These symptoms can be manifested some hours after the consumption of the last dosage of the drug and may last for a week or more.¹² The physical withdrawal symptoms often stop after 14 days.¹³⁻¹⁶ Withdrawal syndrome may impress the patient's impetus for contribution in programs of addiction treatment.¹³ Management of these symptoms can help sufferers to cope with their disease more easily.

In medically assisted opioid withdrawal, treatment with methadone prevents withdrawal symptoms and decreases or deletes craving since its dosage is gradually decreased until the medication is discontinued.¹⁷ Although methadone is considered as the main pharmacotherapy for opioid dependence,^{18,19} the cost of treatment with methadone prevents its medical usage in some parts of South-East Asia.²⁰ One of the alternative medications for the treatment of opioid dependence is tincture of opium (TOP) which is used in some Asian countries for the management of opioid withdrawal syndrome.²¹ It is prepared from opium in alcohol and water and contains 1% morphine. It is used as a traditional medicine in some South-East Asia region. Due to its low cost, TOP is preferred over methadone.²⁰ Given that few studies comparing the efficacy of TOP and methadone in the management of opium withdrawal syndrome,²² the aim of the current study is to compare the efficacy of methadone and TOP in controlling agitation of withdrawal syndrome in opium addicted patients admitted to

the intensive care units (ICUs).

Methods

This clinical trial study was conducted on patients admitted to ICU of Shahid Bahonar Hospital, Kerman, Iran during 2011. This study was approved by the ethics committee (K-90-145) of Kerman University of Medical Sciences. In addition, it was registered in Iranian Registry of Clinical Trials (IRCT) website with number IRCT 201107011836N2.

Patients in the age range 18-60 years who were addicted to opiates such as opium, opium sap, or Shireh [according to Diagnostic and Statistical Manual of Mental Disorders (DSM) -TV-TR criteria] entered the study. Moreover, the exclusion criteria were patients addicted to drugs except opium, pregnancy, lactation, and liver, heart, and kidney failure.

After taking consent from the patients or their relatives, 66 opiate addicted patients were selected from Shahid Bahonar Hospital and finally 6 patients excluded from the study (2 patients were addicted to other drugs except opium and 4 patients had heart failure). Therefore, the study was conducted on 60 patients. These patients were classified into two parallel groups using block randomization procedure ($n = 30$). The first and second groups respectively consumed methadone syrup (5 mg/ml) and TOP (10 mg/ml) during hospitalization. It is noteworthy that the patients were blind in the current study. Figure 1 shows the CONSORT flow diagram of patients in Shahid Bahonar Hospital.

Results

The type and amount of the drugs consumed were used to calculate the amount of daily morphine intake in each patient according to table 1. Then, the equivalent doses of methadone syrup or TOP were administered for each patient. Furthermore, acetaminophen (15 mg/kg) was administered every 6 hours to control pain in the patients.

The following points are essential for determining the dose of TOP and methadone.²³

1. Pure opium contains about 10 % morphine.
2. Opium sap contains approximately 20 % morphine.
3. The uptake of the morphine content of opium by Vafoor is about 30%. This rate by heated-stone (Sikh-sang method) and oral method is 60% and 60%-90%, respectively.
4. One mesghal of opium is equal to 4-5 g.

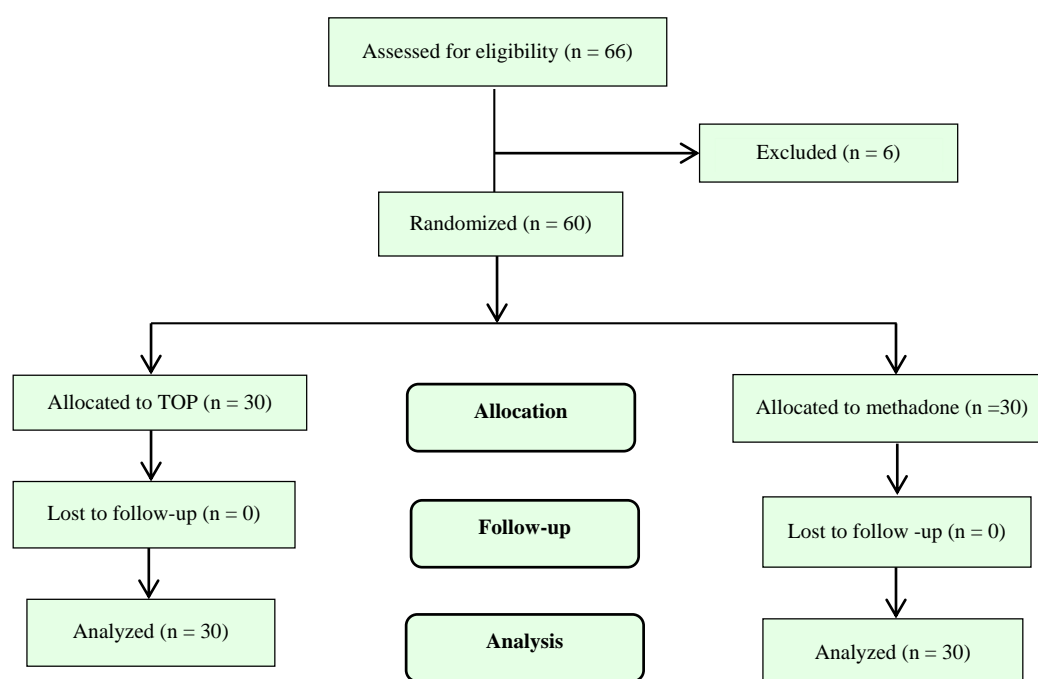


Figure 1. Consort flow diagram of patients in Shahid Bahonar Hospital, Kerman, Iran

Determination of the dose of TOP and methadone syrup in opiate-addicted patients was calculated according to usual opium weight in consumers (Table 1).

Table 1. Conventional weight of opium in opium users and the amount of morphine and methadone equivalent

Unit	Weight used in consumer (mg)	Morphine (mg)	Methadone equivalent (mg)
1 lentils	24.24	2.44	2.44
1 Wheat	48.80	4.88	4.88
1 Pea	195.30	19.35	19.35
1 Mesghal	4687.50	468.75	468.75

Since the half-life of methadone is long, people taking methadone received it twice a day, but the frequency of TOP use was equal to that of opium.

Agitation in these patients was assessed through Richmond Agitation-Sedation Scale (RASS) which is shown in table 2.²⁴

In addition, vital signs including heart rate, body temperature, systolic and diastolic blood pressure, and respiratory rate were checked in each patient.

Data were entered the SPSS software (version 19, SPSS Inc., Chicago, IL, USA). Paired sample t-test was used to compare the variables before and after treatment and the independent t-test was used to compare the two groups.

Table 2. Richmond Agitation-Sedation Scale (RASS)

Score	Terms	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent non-purposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	Alert and relaxed; spontaneously pays attention to caregiver
-1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Results

The mean daily intake of opium was 2.10 ± 0.54 times per day. The mean adsorbed morphine was 28.30 ± 25.70 mg/day. In addition, the mean consumed drug was 1.80 ± 2.38 g/day.

Table 3 shows the frequency distribution of patients in terms of gender, age, type of drug, method of consumption, and administration of drug.

Table 3. Frequency distribution of patients in terms of gender, age, job status, marital status, type of drug, method and administration of drug

Parameters	n (%)
Gender	
Men	48 (80.0)
Women	12 (20.0)
Age	
< 20	3 (5.0)
20-40	28 (46.7)
> 40	29 (48.3)
Job Status	
Unemployed people	25 (41.7)
Employed people	35 (58.3)
Marital status	
Single	18 (30.0)
Married	42 (70.0)
Type of drug	
Opium	53 (88.3)
Opium sap	7 (11.7)
Method	
Opium pipe (locally named Vafoor)	11 (18.3)
Oral	36 (60.0)
Heated-stone (locally named Sikh-sang)	13 (21.7)
Administered medication	
Methadone	30 (50.0)
TOP	30 (50.0)

Comparison of patients in the two groups in terms of demographic data showed that there was no significant difference between the two groups regarding the demographic data ($P > 0.05$).

Frequency distribution of patients in the two

groups in terms of RASS score is shown in table 4.

As shown in table 4, 56.7% of patients in methadone group had RASS score 0, while 80 % of the patients in the TOP group had RASS score 0.

Moreover, a significant difference was seen in the frequency distribution of patients in methadone group in terms of RASS score ($P < 0.010$). In addition, there was a significant difference in the frequency distribution of patients in the TOP group regarding RASS score ($P < 0.010$).

Table 4. Frequency distribution of patients in the two groups in terms of Richmond Agitation-Sedation Scale (RASS) score

Medications		RASS score					P
		-1	0	1	2	3	
Methadone	n	6	17	5	1	1	<0.001
	%	20	56.7	16.7	3.3	3.3	
TOP	n	2	24	4	0	0	<0.001
	%	6.7	80	13.3	0	0	

The effects of methadone on variables including GCS score, respiratory rate, body temperature, systolic and diastolic blood pressure, and heart rate are shown in table 5.

According to table 5, methadone decreased systolic blood pressure, heart rate, respiratory rate, and GCS ($P < 0.05$), but it had no effect on diastolic blood pressure and body temperature ($P > 0.05$).

Table 6 shows the effect of TOP on variables including systolic and diastolic blood pressure, heart rate, respiratory rate, and GCS.

Given table 6, TOP decreased systolic blood pressure and GCS ($P < 0.050$), but it had no effect on diastolic blood pressure, body temperature, heart rate, and respiratory rate ($P > 0.050$).

Comparison of the two groups (methadone and opium groups) regarding the variables including medication dose, systolic and diastolic blood pressure, body temperature, heart rate, respiratory rate, and GCS are shown in table 7.

Table 5. Effect of methadone on variables

Variables	Before treatment	After treatment	P
	Mean \pm SD	Mean \pm SD	
Systolic blood pressure (mmHg)	139.73 \pm 19.78	133.63 \pm 22.31	0.041
Diastolic blood pressure (mmHg)	85.23 \pm 10.43	85.47 \pm 12.24	0.927
Body temperature (Centigrade)	37.42 \pm 0.56	37.29 \pm 0.57	0.255
Heart rate/min	79.10 \pm 13.66	73.20 \pm 18.25	0.044
Respiratory rate	22.07 \pm 5.99	19.30 \pm 6.09	0.017
GCS	11.25 \pm 2.87	12.32 \pm 3.019	0.033

SD: Standard deviation; GCS: Glasgow Coma Scale

Table 6. Effect of tincture of opium (TOP) on variables

Variables	Before treatment	After treatment	P
	Mean \pm SD	Mean \pm SD	
Systolic blood pressure (mmHg)	130.27 \pm 32.31	127.07 \pm 20.79	0.041
Diastolic blood pressure (mmHg)	79.63 \pm 16.19	76.53 \pm 13.45	0.192
Body temperature (Centigrade)	37.57 \pm 0.57	37.40 \pm 0.17	0.123
Heart rate/min	89.17 \pm 18.22	84.64 \pm 15.27	0.191
Respiratory rate	19.43 \pm 4.45	18.70 \pm 4.46	0.441
GCS	11.10 \pm 2.83	12.90 \pm 2.04	< 0.001

SD: Standard deviation; GCS: Glasgow Coma Scale

As shown in table 7, there was no significant difference between the two groups in terms of the systolic and diastolic blood pressure, GCS score, body temperature, heart rate, and respiratory rate ($P > 0.050$). However, significant a difference was observed between the two groups regarding the dose of medication ($P < 0.010$). Furthermore, comparison of patients in the two groups in terms of side effects showed that gastrointestinal complications were observed in 3.3 % of patients in the TOP group.

Discussion

After hospitalization, patients treated with opioids suffer from opium withdrawal syndrome due to discontinuation of opium.²⁵ Feeling restlessness in hospitalized patients delays recovery, increases length of hospital stay, and ultimately increases morbidity and mortality. It is desirable to use a suitable alternative drug that can control the symptoms of restlessness with lower doses and least side effects. Several studies have shown the role of morphine and methadone in controlling opium withdrawal syndrome in patients addicted to opium.^{26,27} The use of morphine is not desirable because of the need for an infusion pump device and continuous administration, low half-life, and drug accumulation in the body.^{26,27}

To treat opium withdrawal syndrome, injectable methadone is mainly used. However, in the present study, oral forms of the two medications (oral methadone and TOP) were used because the injection process was thought to be aggressive.

Considering the RASS score, the findings of the current study showed a significant difference between the two groups after treatment. It seems that both drugs improved patients' restlessness. Although methadone and TOP could improve vital signs in patients, no significant difference was observed between the two groups in this regard. It can be claimed that the effect of the two drugs on the vital signs was almost similar. However, a significant difference was seen between the two groups in terms of medication dose. It was found that the lower dose of methadone, in comparison with TOP was needed to control patients' restlessness and vital signs.

In a study by Aghdaie et al., injectable methadone was used for the treatment of opium addicted patients hospitalized in ICUs. The findings showed that symptoms of opium withdrawal syndrome were controlled in 80.83% of patients.²⁵ Additionally, Dyer et al. reported that methadone was effective for controlling withdrawal syndrome in heroin addicted patients.²⁸

Most studies compared the effect of morphine and methadone on agitation of withdrawal syndrome. For example, Mirinezhad et al. assessed the effect of morphine and methadone on pulmonary function of patients who were hospitalized in ICU and observed that the use of methadone was preferred to morphine since it caused no dependency on medication after being discharged from ICU and it was associated with easy ambulation.²⁶

Table 7. Comparison of the two groups regarding variables

Variables	Methadone group (Group 1)	Opium group (Group 2)	P
	Mean \pm SD	Mean \pm SD	
Medication dose (mg)	36.17 \pm 26.99	112.67 \pm 102.74	< 0.001
Systolic blood pressure (mm Hg)	-6.10 \pm 15.65	-3.20 \pm 21.13	0.548
Diastolic blood pressure (mm Hg)	0.23 \pm 13.74	-3.10 \pm 12.70	0.333
Body temperature (centigrade)	-0.13 \pm 0.63	-0.17 \pm 0.58	0.816
Heart rate/ min	-5.90 \pm 15.36	-4.53 \pm 18.54	0.757
Respiratory rate	-2.77 \pm 6.00	-0.73 \pm 5.14	0.164
GCS	1.07 \pm 2.52	1.80 \pm 2.43	0.267

SD: Standard deviation; GCS: Glasgow Coma Scale

Ripamonti et al. investigated the effect of morphine and oral methadone on the treatment of pain and observed a strong linear positive relationship between morphine and methadone equianalgesic doses. The findings showed that oral methadone was stronger than morphine.²⁹ On the other hand, Pollock et al. compared methadone and morphine efficacy and reported a lack of consensus for replacing morphine with methadone.³⁰

Lainwala et al. compared the effect of methadone and morphine administration on length of hospital stay and reported no significant difference.³¹

Few studies evaluated the role of TOP and methadone in controlling patient's agitation because of withdrawal syndrome. Tabassomi et al. compared the impact of methadone syrup and TOP on the management of opium withdrawal syndrome. Although they observed no significant difference between the two groups regarding opioid withdrawal scale, TOP was considered as a potential alternative to methadone syrup for suppressing opium withdrawal symptoms with minimal adverse effects.³² The findings of the present study were not consistent with those revealed by Tabassomi et al.³² Jittiwutikarn et al. reported that TOP was not as good as methadone

for preventing withdrawal syndrome,²⁰ which was not consistent with the current study.³² However, it was specified that substitution of opium by methadone syrup and TOP could prevent toxicity of opium due to impurities, including lead.³³

Conclusion

According to the results of the current study, lower dose of methadone, compared to TOP, could control agitation caused by opium withdrawal symptoms.

Conflict of Interests

The authors have no conflict of interest.

Acknowledgements

The authors would like to appreciate the staff of ICU of Shahid Bahonar Hospital of Kerman for their support and contribution to this study.

Authors' Contribution

SMS and MA designed current study. MP and RS and FS collected data and played a main role in writing of manuscript.

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مقایسه اثربخشی متادون و تنتور تریاک در کنترل بی‌قراری ناشی از سندرم ترک در بیماران معتاد به تریاک در بخش مراقبت‌های ویژه: یک کارآزمایی تصادفی

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مقاله پژوهشی

چکیده

مقدمه: با توجه به این که مطالعات کمی با هدف مقایسه کارایی متادون و تنتور تریاک (Tincture of opium یا TOP) در کنترل بی‌قراری ناشی از سندرم ترک انجام شده است، هدف از انجام پژوهش حاضر، ارزیابی مقایسه تأثیر متادون و TOP در کنترل بی‌قراری ناشی از سندرم ترک در بیماران معتاد به تریاک در بخش مراقبت‌های ویژه (ICU یا Intensive care unit) بود.

روش‌ها: این تحقیق از نوع کارآزمایی بالینی بود که بر روی ۶۰ بیمار بستری در بخش ICU بیمارستان شهید باهنر کرمان انجام شد. پس از تقسیم بیماران به دو گروه، در گروه اول شربت متادون (۵ میلی‌گرم در میلی‌لیتر) و در گروه دوم TOP (۱۰ میلی‌گرم در میلی‌لیتر) مورد استفاده قرار گرفت. درجه اضطراب در این بیماران به وسیله مقیاس بی‌قراری- آرامش (Richmond Agitation-Sedation Scale) Richmond یا (RASS) ارزیابی گردید. علایم حیاتی نیز مورد بررسی قرار گرفت. به منظور تجزیه و تحلیل داده‌ها، از آزمون‌های Paired t و Independent t استفاده شد.

یافته‌ها: دز تجویز متادون و TOP به ترتیب $26/99 \pm 36/17$ و $102/74 \pm 112/67$ میلی‌گرم بود ($P < 0/010$). تجویز متادون منجر به کاهش معنی‌دار علایم حیاتی بیماران از جمله فشار خون سیستولیک، ضربان قلب، ضربان تنفسی و مقیاس اغمای (Glasgow Coma Scale) Glasgow یا (GCS) شد ($P < 0/050$). اگرچه تجویز TOP فشار خون سیستولیک و GCS را به میزان قابل توجهی کاهش داد ($P < 0/050$)، اما هیچ تأثیری بر فشار خون دیاستولیک بیماران، درجه حرارت بدن، ضربان قلب و ضربان تنفسی بیماران نداشت ($P > 0/050$). در مجموع، از نظر علایم حیاتی بین دو گروه اختلاف معنی‌داری مشاهده نشد ($P > 0/050$)، اما از نظر نمره RASS اختلاف بین گروه متادون و TOP معنی‌دار بود ($P < 0/010$).

نتیجه‌گیری: با توجه به نتایج، دز کمتری از متادون در مقایسه با TOP، می‌تواند باعث کنترل بی‌قراری ناشی از علایم ترک تریاک شود.

واژگان کلیدی: متادون؛ اعتیاد به تریاک؛ واحد مراقبت‌های ویژه

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تاریخ پذیرش: ۱۳۹۸/۱۰/۲۸

تاریخ دریافت: ۱۳۹۸/۹/۱

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